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(54) Title: POLYPEPTIDES AND THEIR USE IN TREATMENT AND PROPHYLAXIS OF AUTO-IMMUNE DISEASE		
(57) Abstract <p>The invention relates to polypeptides and fragments thereof, to their use in the prevention, diagnosis and treatment of auto-immune disease such as rheumatoid arthritis (RA), and to methods of preparing these fragments. Examples of such polypeptides include fragments of human heat shock protein hsp58. The invention provides a polypeptide of up to 21 amino acid residues which comprises or consists of the following sequences: (1) VGLTLENADLSL (SEQ ID 107), (2) VLNRLKVGLQV (SEQ ID 108), (3) LTLNLEDVQPHD (SEQ ID 110) or a homologue or functional equivalent or mimetic thereof. The invention provides a vaccine for the prophylactic or therapeutic treatment of RA which comprises a polypeptide as described above.</p>		

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POLYPEPTIDES AND THEIR USE IN TREATMENT AND PROPHYLAXIS OF
AUTO-IMMUNE DISEASE

The present invention relates to polypeptides and fragments thereof, to their use in the prevention, diagnosis and treatment of auto-immune disease such as rheumatoid arthritis, and to methods of preparing these fragments.

Autoimmune diseases are thought to arise as a result of similarities between a foreign molecule or antigen and a molecular structure of the organism itself. Chronic forms of arthritis are thought to involve autoimmunity to constituents of the joints in particular of the connective tissues of the body.

Rheumatoid arthritis (RA) is the most common of the arthritides which exhibit autoimmune manifestations [reviewed in Elson et al, Autoimmunity (1992) 13:327]. The disease is the third most common of the elderly and causes a tremendous burden of pain and suffering. It has been known for some time that an association exists between HLA-DR4 and RA suggesting a T-cell involvement [Stasney, New Eng. J. Med. (1978) 298:869 and Watanabe et al, J. exp. Med. (1989) 169:2263] and a genetic contribution to the disease. However, recent twin studies [Silman et al, Brit. J. Rheumatol. (1993) 32:903] have suggested that the upper limit of the genetic

contribution is only 15%. It follows that the main factors contributing to the induction of RA are environmental. This contention is supported by the increased incidence of RA in South Africans as they move from villages to towns [Solomon et al, Ann, rheum. Dis. (1975) 34:128] and the increasing evidence of abnormal immune responses to microbes in patients with the disease [Deighton et al, Brit. J. Rheumatol. (1992) 31:241]. Such considerations have led to the suggestion that RA is triggered by bacterial or viral antigens which may share a high degree of homology with self protein [reviewed in reference McCulloch et al, Clin. Exp. Immunol. (1993) 92:1].

One model has proved useful in investigating environmental factors which contribute to the disease is pristane-induced arthritis (PIA). This model is based upon the finding that a proportion of mice injected intraperitoneally with the paraffin oil pristane (2, 6, 10, 14-tetramethylpentadecane) develop a chronic T-cell dependent inflammatory arthritis between 60 and 200 days later depending on the strain of mice [Potter M, J. Immunol. (1981) 127:1591, Bedwell et al, J. Immunol. (1987) 25:393, Wooley et al, Arthritis. Rheum. (1987) 32:1022, Wooley et al, Arthritis. Rheum. (1989) 32:1022 and Levitt et al, J. Rheumatol. (1992) 19:1342]. The time course of PIA thus distinguishes it from other established animal models resembling RA such as adjuvant

arthritis, streptococcal cell wall arthritis and collagen-induced arthritis. Histopathologically the arthritis is characterised by cell infiltration and synoviocyte hyperplasia with cartilage erosions and the formation of pannus [Bedwell et al, J. Immunol. (1987) 25:393, Hopkins et al, Rheumatol. Int. (1984) 5:21 and Thompson et al, Imm. Let. (1993) 36:227].

Recent work has demonstrated that the microbial environment influences the development of PIA. Specific pathogen free (SPF) mice maintained under sterile conditions in an isolator are resistant to the development of PIA whilst the return of such animals to a conventional environment restores their susceptibility to the induction of the disease [Thompson et al, Imm. Let. (1993) 36:227]. Although the resident bowel flora differs between susceptible and refractory mice [Thompson et al, Imm. Let. (1993) 36:227], it is not known if this change affects susceptibility to the disease or indeed how exposure to microbes renders mice susceptible to the development of PIA. However, it is known that serum of mice with PIA contains raised levels of antibodies to the immunodominant mycobacterial 65kD heat shock protein (hsp65) as compared with age matched normal animals or pristane injected mice which failed to develop the disease.

It has long been recognised that heat shock proteins

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(hsp's) are immunodominant antigens in a number of infectious diseases, such as tuberculosis and leishmania. These infectious diseases can have similar abnormalities as observed in RA such as raised agalactosyl-IgG levels, the organs involved and range of autoantibodies present. Since environmental factors are clearly important in RA, microbial agents and hence hsp's were implicated.

Hsps are grouped in gene families according to their molecular weight and sequence homology within individual groups. For example, hsp60 (60KD) gene family includes members hsp65 (mycobacterial) and hsp58 (mammalian).

It was found that splenic T-cells from arthritic mice proliferate more vigorously in vitro in response to hsp65 than T-cells from age matched normal or non-arthritic mice. Furthermore, if the mice are immunised with hsp65 in incomplete Freud's adjuvant (IFA) prior to pristane challenge, the disease will not develop [Thompson et al, Eur. J. Immunol. (1990) 20:2479 and Thompson et al, Autoimmunity, (1991) 11:89]. This protective effect is specific to hsp65 and is not induced by the E.coli equivalent GroEl or other unrelated antigens [Thompson et al, Eur. J. Immunol. (1990) 20:2479] and cannot be attributed to antigenic competition [Barker et al, Autoimmunity. (1992) 14:73]. These findings raise the possibility that mice become sensitised to hsp by exposure to microbial flora in the environment and that

this process is necessary for the induction of arthritis by pristane injection. If so, it would be predicted that there is a relationship between sensitisation to hsp65 and susceptibility to PIA. Experiments carried out by the applicants suggest that this hypothesis is correct.

One possibility which would explain how PIA could develop from such sensitisation is that pristane promotes an immune response to epitopes on microbial hsp65 which cross react with self (mammalian) hsp58 [Thompson et al, Imm. Let. (1993) 36:227 and Thompson et al, Eur. J. Immunol. (1990) 20:2479]. This suggestion gains credence from the fact that hsps are dominant antigens in the immune response to microorganisms, despite their extraordinarily high sequence conservation throughout the eukaryotic and prokaryotic kingdoms [Cohen et al, Immunol. Today, (1991) 12 105]. Thus, every microbial hsp is studded with self epitopes for any animal with an immune system. Moreover, they are normal constituents of all cells although their synthesis is increased by many different forms of cellular stress. Since hsp 58 has been detected in the joints of patients with RA [Karlsson-Parra et al, Scand. J. Immunol. (1990) 31:283] and T-cells from mice with PIA react with joint extracts [Thompson et al, Eur. J. Immunol. (1990) 20:2479] it seems reasonable to postulate that hsp58 could be a target antigen in the joints of mice developing PIA. This hypothesis may explain the paradox that both mice with PIA and animals protected from the development of arthritis by hsp65 preimmunisation exhibit elevated

immune responses to the 65kD mycobacterial heat shock protein. It would be expected that only mice with PIA should develop autoimmune responses to the 60kD family of hsps whereas the response of mice pre-immunised with hsp65 should be restricted to microbial specific determinants. In other words, the response elicited by immunisation with hps65 in IFA differs from that induced by sensitisation with environmental/bowel microorganisms.

T cell-mediated response to mycobacterial antigens has been implicated in the pathogenesis of inflammatory arthritis both in experimental animal models and in man. In adjuvant arthritis in rats, it has been established that the disease can be initiated by T cell clones specific for the 65-kDa mycobacterial heat-shock protein.

Rats may also be protected to subsequent adjuvant arthritis induction by pre-immunisation with either a 65 KDa specific T cell line or with the hsp itself (Van Eden et al., Nature, 1988, 331:171 and Holoshitz et al., Science 1983, 219:56).

The epitope recognised by the arthritogenic T cell clone has been localized to amino acids 180-188. EP-A-322990 describes polypeptides having amino acid sequence 172-192 of a bacterial hsp 64 and their use as immunogens for inducing resistance to auto-immune disease. WO 92/04049 discloses that a peptide comprising the amino acid

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sequence corresponding to positions 180-186 of the Mycobacterium tuberculosis protein hsp65 is effective in the prevention and treatment of immune-related disease such as autoimmune arthritis.

Using the PIA model, it has been found (Thompson et al. Eur. J. Immunology, 1990, 20: 2479-2484) that autoimmune reactions to an antigen which cross-reacts with hsp65 are generated in pristane-induced arthritis. Furthermore, pre-immunisation with hsp65 has been shown to protect mice from the development of pristane-induced arthritis by altering the specificity or quality of the immune response to this antigen.

On further study using the PIA model, the applicants were surprised to find that a region of the microbial protein hsp65 quite different and remote from that described in for example WO 92/04049 is effective in providing a protective response against arthritis.

In a first aspect, the present invention provides a polypeptide of up to 21 amino acid residues which comprises or consists of the sequence

VGLTLENADLSL

(SEQ ID 107)

or a homologue or functional equivalent or mimetic thereof. The above described polypeptide sequence corresponds to amino acids 302-314 of microbial (mycobacterial) hsp65. The invention also provides the use of such a polypeptide in the prophylaxis or treatment of auto-immune disease such as RA.

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Most of the previous work in this area has been carried out using hsp from microbial sources since there are obvious dangers in considering the administration of 'self-antigens' in the treatment of auto-immune disease in that such antigens may increase the harmful T cell response, to the detriment of the patient.

The applicants formed a view that the role of microbial hsp's in both the induction of arthritis and protection against the disease may be due to the form of antigen presentation. Depending upon this, either T_H1 cells are induced which leads to pristane induced arthritis due to determinant spreading, or T_H2 cells are induced which leads to protection due to repertoire limitation. Assuming this to be correct, the mode of application of the immunogenic agent would have a considerable effect on this. Indeed, it has been shown (Thompson et al., Immunology 1993, 79 152-157) that type II collagen (another potential joint antigen) when administered orally, lowered both the incidence and severity of pristane-induced arthritis whereas intraperitoneally administered type II collagen exacerbated both.

The applicants decided to investigate whether the human homologue of microbial hsp65, hsp58, and fragments thereof may be employed in the prophylaxis or therapy of

RA. A trans-mucosal membrane mode of administration would preferably be employed. Full sequence information in respect of human hsp58 is known for example from Jindal et al. Mol. Cell Biol. 1989, 9:2279-2283. It is therefore proposed that human hsp58 or fragments thereof are useful in the prophylaxis or treatment of RA.

Hence the present invention provides the use of human hsp58 or a fragment thereof containing or consisting of the amino acid sequence

VLNRLKVGLQV

(SEQ ID 108)

or a homologue or functional equivalent or mimetic thereof in the prophylaxis or treatment of auto-immune disease such as RA; and provides novel polypeptide fragments of up to 21 amino acid residues, per se.

It is believed by analogy with work carried out using microbial hsp65; that the region of hsp58 containing amino acid residues corresponding to 261-271 of hsp65 is important for this application.

This region is a non-conserved region and is mammalian specific. This means that the region will not cross-react with the bacterial form of the protein and administered transmucosally, would induce T-cell tolerance to it and thus prevent arthritis.

Hence the present invention further provides a

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polypeptide of up to 21 amino acid residues comprising or consisting of the sequence

VLNRLKVGLQV

(SEQ ID 108)

or a homologue or functional equivalent or mimetic thereof.

Examples of such polypeptides include fragments of human hsp58 protein, in particular those including the amino acid residues corresponding to 271-267 of hsp65 or homologues thereof; i.e. the amino acid sequence

DVDGEALSTLVNRLKV

(SEQ ID 109)

A particularly preferred polypeptide will consist only of the amino acids VLNRLKVGLQV.

It is believed by analogy with work carried out using microbial hsp65, that the region of hsp58 containing amino acid residues corresponding to 302-314 of hsp65 is also important for this application. This region is also a non-conserved region and is mammalian specific.

The present invention further provides the use of human hsp58 fragment containing or consisting of the amino acid sequence

LTLNLEDVQPHD

(SEQ ID 110)

or a homologue or functional equivalent or mimetic thereof in the prophylaxis or treatment of auto-immune disease such as RA; and provides novel polypeptide fragments of up to 21 amino acid residues, per se.

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Hence the invention further provides a polypeptide of up to 21 amino acid residues comprising or consisting of the sequence

LTLNLEDVQPHD (SEQ ID 110)

or a homologue or functional equivalent or mimetic thereof.

A particularly preferred polypeptide will consist only of the amino acids

LTLNLEDVQPHD

The polypeptides of the invention have been found to have a prophylactic or therapeutic effect when applied immunogenically in the treatment of RA.

Hence the invention further provides a vaccine for the prophylactic or therapeutic treatment of RA which vaccine comprises a polypeptide as described above. For use in the treatment, the polypeptide is suitably administered in a trans-mucosal membrane manner for example, orally or nasally. Alternatively the polypeptide may be formulated as a suppository.

Administration in this way should cause the polypeptide to act in a prophylactic or therapeutic way to reduce the symptoms of RA. The mechanism by which this effect is produced is not understood. It is possible that these polypeptides act as non-specific downregulators of the immune response. The mechanism of oral tolerance has

not been fully elucidated but antigen-driven bystander suppression after oral administration of antigens has been proposed (Miller et al., J. Exp. Med. (1991) 144 791-798).

The polypeptides of the invention are suitably administered in the form of a pharmaceutical composition in combination with a pharmaceutically acceptable carrier or excipient. Such compositions form a further aspect of the invention.

Suitable carriers include solid or liquid carriers. Examples of formulations including solid carriers include tablets or suspensions for oral administration or suppositories. Suitable liquid carriers include oils or water. The compositions may be adapted for nasal administration by inhalers, atomizers or sprays as are available in the art.

In suitable circumstances it may be desirable or necessary to administer the polypeptide, or a pharmaceutical composition including the polypeptide, parenterally, for example subcutaneously, intramuscularly, intravenously or intraperitoneally.

The polypeptides of the invention can be produced using various techniques which would be apparent to the skilled person. For example, they may be obtained by

fragmentation of human hsp58 using conventional techniques after which the desired fragments obtained by purification, again using techniques which are known in the art. However peptides obtained by this method are less likely to have the precisely the desired length.

Alternatively, the polypeptides may be obtained using recombinant DNA technology. The nucleotide sequence encoding the desired polypeptide can be incorporated into a suitable host using a vector system which causes expression of the polypeptide.

Preferably however, polypeptides sequences may be generated entirely synthetically using standard chemical methods or peptide synthesizers available in the art.

As used herein, the expression 'homologue' refers to peptides having an amino acid sequence which is are at least 60%, preferably 70% and most preferably at least 80% homologous to the described polypeptide. The expression 'functional equivalent' or 'mimetic' relates to any chemical, which may be a peptide or other organic chemical which produces similar effects in vivo to the compounds of the present invention. In particular, such compounds will produce a protective immunogenic response against RA when applied in pristane-induced arthritis model using tests as described in the examples hereinafter.

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The observations and deductions which led to the present invention will now be outlined with reference to the accompanying drawings in which:

Figure 1 is the peptide library comprising eleven pools of overlapping peptides corresponding to the entire sequence of microbial hsp65. (SEQ IDs Nos. 1-106)

Figure 2 shows a comparison of the proliferative response of T cells from each of 6 arthritic mice (top panel), 6 protected mice (middle panel) and 6 normal mice (n=6) to the eleven pools of overlapping peptides defined in Figure 1;

Figure 3 shows the results of studies to determine the protection against PIA of mice pre-immunised with microbial hsp65 polypeptides;

Figure 4 shows the entire amino acid sequence of human hsp58 (top line) in corresponding relationship to the entire sequence of microbial hsp65 (lower line);
(SEQ IDs Nos. 107-109)

Figure 5 shows the sequences and % homology of 5 peptides in the region hsp65 m 251-312 and the corresponding sequences of hsp58; (SEQ IDs Nos. 110-117)

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Figure 6 shows the therapeutic effect of immunisation with polypeptides of the invention at 60 days post pristane injection (D=60); and

Figure 7 shows the prophylactic effect of pre-immunisation with polypeptides of the invention at 10 days prior to pristane injection (D=-10).

Experiment 1

Proliferation of T cells in-vitro from PIA mice, hsp65 protected mice and normal age-matched mice.

Animals. Male CBA/Igb mice aged between 4 and 8 weeks were used unless otherwise specified. CBA/Igb mice were obtained by back-crossing (101 strain x CBA) F1 hybrids to CBA mice and selecting those mice with Igb allotype in their serum.

Arthritis induction by pristane. One group of six mice were immunised intraperitoneally with 50 micrograms of mycobacterial hsp65 administered as an emulsion in incomplete Freuds adjuvant (IFA). This group formed the protected group of mice. After ten days, this group and a further group of 6 mice received two intraperitoneal injections of 0.5ml of pristane 50 days apart (Aldrich

Chemical Co., Milwaukee, WI.) in order to induce arthritis. A final group of 'normal' mice were maintained as controls.

Synthetic peptides used as antigens in immunisation studies. A library consisting of 106 overlapping peptides, representing the complete sequence of microbial hsp65, of between 15 and 19 amino acids in length, was synthesised using a simultaneous multiple-peptide solid phase synthetic method [Houghton R.A. Proc. Natl. Acad. Sci. USA. (1985) 82:5131] using a polyamide resin [Arshady et al, J. Chem. Soc. Perkin Trans. (1981) I.529] and Fmoc chemistry. The complete library is shown in Figure 1. Completed peptides were extracted from the resin using trifluoroacetic acid and suitable scavengers, and isolated by solvent evaporation and precipitation with methanol and diethylether. Purity was checked by amino acid analysis and by HPLC. Irrelevant control antigens BSA and human IgG were also used along with the mitogen ConA.

Eleven antigens were prepared, each comprising a pool of the groups of polypeptides, set out in Figure 1 as groups 1-11.

Preparation of T-cells and APC for culture. After 200 days, spleens of individual mice were aseptically removed and single cell suspensions made in a Petri dish containing RPMI-1640 medium supplemented with 20mM HEPES (pH 7.2, Flow Labs). Erythrocytes were removed by

treating the spleen cells with 0.83% (w/v) NH_4Cl solution buffered with Tris (pH 7.2). After washing, cells were suspended in RPMI-1640 HEPES at 1.25×10^6 cells/ml. Responder T cells were enriched according to the panning method of Engleman et al [Engleman et al. J. Immunol. (1981) 127:2124]. Briefly, 10cm diameter Petri dishes (Sterilin Ltd., Hounslow, GB) were coated with 5ml of 0.5 mg/ml mouse γ -globulin in PBS at room temperature for 2 hrs. After washing once with PBS, Petri dishes were incubated with 5ml of a 1/100 dilution of rabbit anti-mouse Ig serum at 4°C overnight. After washing, 8ml of the spleen cell suspensions (1×10^6 cells) were poured into the mouse Ig-rabbit anti-mouse Ig coated Petri dishes and incubated at room temperature for 40 mins. The nonadherent cells were then gently aspirated followed by washing with medium. These cells were then used as the T cell enriched fractions. A purity of .85% was achieved as assessed by anti-Thy 1.2 staining using flow cytometry (FACScan, Becton Dickinson Ltd., Oxford, GB). Normal mouse spleen cells were used as antigen presenting cells. In these experiments the APC were irradiated 1000 rads from a caesium source (Gravatom Industries, Gosport, GB).

Culture and assay of proliferation. This was carried out as described in Thompson et al., supra. The medium employed was alpha modification of Eagle's medium (alpha MEM) (Flow) supplemented with 4mM L-glutamine (Flow), 100U/ml benzyl penicillin (Glaxo Ltd., Green ford, GB),

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100µg/ml streptomycin sulphate (Evans Medical Ltd., Greenford, GB), 5×10^{-5} M2-mercaptoethanol (Sigma), 20 mM HEPES and 0.5% fresh normal mouse serum. The cultures consisted of 1.25×10^6 purified splenic T-cells plus 1.25×10^6 APC per ml, in a volume of 2ml in a 24 well plate (Flow) in the presence or absence of the various antigens 92.5-10µg/ml). Alternatively, some cultures were set up in a volume of 200µl in round bottom 96 well plates (Flow). All cultures were incubated at 37°C in a humidified atmosphere of 5% CO₂ and 95% air.

After the periods of incubation indicated, triplicate 100microlitre samples of each of the 2 ml cultures were transferred to 96 well, round bottom culture plates (Flow) and pulsed with 2mCi of ³H-Thymidine (specific activity 70-85 Ci/mMol; Amersham International Ltd., Amersham, GB) per well for 6 hours. The cells were then harvested onto glass fibre filter mats (Whatman Ltd., Maidstone, GB) using a multiple sample harvester (Skatron AS, Lier, Norway) and the ³H-Thymidine incorporated into newly synthesized DNA measured using conventional liquid scintillation procedures with a LKB rackbeta counter (LKB-Wallac Ltd., Pharmacia, Uppsala, Sweden). The results are presented (Figure 2) as stimulation indices (S.I. = cpm test divided by cpm control without antigen). Positive stimulation resulted in maximal ³H-Thymidine uptake of ~30,000 counts per minute.

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Experiment 2

Protection of mice against PIA by immunisation with microbial Hsp65 fragments

Animals. Male CBA/Igb mice aged between 4 and 8 weeks as described in Experiment 1 were used unless otherwise specified.

Immunisation of animals. Groups of mice were immunised intraperitoneally 10 days before pristane challenge as follows:

Group	No. mice	pre-immunisation polypeptide
1	21 (6 weeks old)	-
2	21 (10 weeks old)	-
3	21	polypeptide corresponding to amino acids 302-314 of microbial hsp 65
4	15	whole microbial hsp65

50 Micrograms of each polypeptide was administered as an emulsion in IFA. The polypeptide fragment used in the pre-immunisation of group 3 was manufactured by

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Cambridge Research Biochemicals of Northwich, Cheshire,
UK.

Arthritis induction by pristane. Arthritis was then induced as described in Experiment 1 by two intraperitoneal injections of 0.5ml of pristane 50 days apart. The animals were examined for the incidence of arthritis in the ankle joints at various time points. The final incidence was assessed 200 days post pristane injection. The arthritis was assessed by measuring the ankle joints with a micrometer. In CBA/Ig^b mice the swollen joints ranged in size from 3.0-4.0mm compared with normal joints which had a range from 2.5-2.8mm. However, this difference could easily be distinguished, and in most experiments the joints were assessed visually, arthritis being scored as present or absent [Thompson et al, Eur. J. Immunol. (1990) 20:2479 and Barker et al, Autoimmunity. (1992) 14:73].

The percentage of animals in each group which developed arthritis after a period of 200 days is shown in Figure 3. It is clear that the peptide region corresponding to 302-314 of hsp65 generates an improved protective effect against RA in mice than when whole hsp65 is applied and confirms that this sequence, which is

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is effective in producing a beneficial effect.

The present inventors have shown in a co-pending application that amino acids 261-271 of microbial hsp65 can be useful in prophylaxis or treatment of auto-immune disease.

In view of the above-mentioned results it is clear that another region of microbial hsp65 which can effectively be used in an immunisation programme is that corresponding to amino acids 302-314 in the sequence. On looking at the corresponding regions of the human homologue hsp58 which, as mentioned above, is non-conserved and so will not cross-react with microbial hsp65, it appears that these will also have a useful effect, provided they can be administered in a 'safe' manner. By analogy with the work using type II collagen, it would seem that administration using a trans-mucosal membrane route, such as oral or nasal application could be appropriate.

To assist comparison between the amino acid sequence of microbial hsp65 (Figure 1) and the sequence of human hsp58, Figure 4 shows the two complete sequences in corresponding alignment, with hsp58 above hsp65. Note that the numbering of hsp65 amino acids is used herein. References herein to amino acid sequence numbers for human fragments (from hsp58) are the numbers of the corresponding hsp60 sequence region. Thus, for example, reference herein to human hsp58 region h 261-271 corresponds to microbial m 261-271 but is, in fact, amino acid 287-297 of the upper sequence of Figure 4.

Likewise, h 302-314 corresponds to m 302-314 but is, in fact, amino acids 330-341 of the upper sequence of Figure 4.

In order to highlight the non-conserved nature of the regions m 261-271 and m 302-314 in comparison to the corresponding regions of the human hsp58 sequence, Figure 5 tabulates the % homology of 5 sequences of the complete region covered by hsp65 m 251-312.

Example 1

Protection of mice against PIA by oral immunisation with human hsp58 fragment.

The eleven amino acid polypeptide of sequence VLNRLKVGLQV (h 261-271):SEQ ID 108) was prepared for use in the Example by Cambridge Research Biochemicals, Gadbrook Par, Nothwich, Cheshire, UK. This polypeptide can then be used to demonstrate the invention using the following methods.

Male CBA/Igb mice aged between 4 and 8 weeks are suitably used. Arthritis can be induced by two intraperitoneal injections of 0.5ml of pristane 50 days apart as described above. Mice which are to be subjected to an immunisation regime are given oral doses of polypeptide dissolved in saline, administered orally with

the aid of a rigid cannula inserted via the oesophagus directly into the stomach. Each animal should receive a single dose on 5 consecutive days (up to and including the day of challenge with pristane) of 50 micrograms of polypeptide.

The mice can be examined visually for the incidence of arthritis in the tarsal (ankle) joints at various time points. This may be assessed for example using a micrometer and comparing enlarged joints with normal joints. In this way, the protective effect of the polypeptide can be demonstrated.

Suitably the experiment is terminated 200 days after pristane injection. After death, stifle (knee) joints may be dissected out, fixed in neutral-buffered formalin and decalcified. If longitudinal sections are prepared and stained with haematoxylin and eosin, arthritis may be further assessed, for example by a veterinary pathologist. Suitably the assessment is carried out blind and joint changes graded according to the following system:

0. Normal.
1. Synovial hyperplasia with pannus formation and mild inflammation (polymorphonuclear leucocytes-PMN) or non-inflammatory mild articular cartilage degeneration.
2. Articular cartilage degeneration with synovial hyperplasia and pannus formation. Moderate to severe inflammation (PMN and macrophages).
3. Articular cartilage degeneration with synovial hyperplasia and pannus formation. Severe inflammation (PMN and macrophages). Significant inflammation in joint space with PMN, macrophages and debris.

In addition, a proliferative T-cell assay may be carried out as described in Experiment 1 above which will further confirm the effectiveness of this polypeptide.

Example 2

Protection of mice against PIA by nasal immunisation with human hsp65 fragment.

Example 1 may be repeated except that instead of oral administration, the polypeptide is given nasally. For this purpose, the animal is first anaesthetized and then laid on its back. A 50 microlitre drop of solution containing 50micrograms of the polypeptide described in Example 1 are then placed on the nostrils. As soon as the animal becomes conscious, the drop is rapidly inhaled. This procedure is repeated five times on five consecutive days in the same way as the oral dosing described in Example 1.

Monitoring of the animals may be carried out in the same way as described above, whereupon a protective effect is shown.

Figure 6 shows the therapeutic effect of administration of polypeptides according to the invention 60 days after first administration of pristane. 50 milligrams of peptide was administered ip as an emulsion IFA to each mouse at day 60. This was after two pristane injections, 50 days apart, one at day 0 and one at day 50. This timing is judged to be just prior to the development/onset phase of PIA. The percentage arthritis was assessed by visual scoring with the assessment being made at the 210th day (D=210). As can be seen from the figure, each of the peptides according to the invention produces a reduction in percentage arthritis in comparison to the control (IPP only).

Figure 7 shows the prophylactic effect of pre-immunisation with peptides according to the invention 10 days prior to the first pristane injection. From these results it appears that h 261-271 may actually increase the incidence of PIA whereas h 302-314 may have little or no effect in reduction of arthritis. However, m 302-314 clearly appears to give a significant reduction or nearly 4 fold in the percentage arthritis.

These data indicate that some polypeptides of the invention may be useful in prophylaxis, some may be useful in treatment, and some may have both prophylactic and therapeutic activity although not all polypeptides of the invention are expected to show both activities.

SEQUENCE LISTING

(1) GENERAL INFORMATION:

(i) APPLICANT:

- (A) NAME: PEPTIDE THERAPEUTICS LIMITED
- (B) STREET: 321 CAMBRIDGE SCIENCE PARK
- (C) CITY: CAMBRIDGE
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(ii) TITLE OF INVENTION: Polypeptides and their use in the
Treatment
and Prophylaxis of Auto-immune Disease

(iii) NUMBER OF SEQUENCES: 117

(iv) COMPUTER READABLE FORM:

- (A) MEDIUM TYPE: Floppy disk
- (B) COMPUTER: IBM PC compatible
- (C) OPERATING SYSTEM: PC-DOS/MS-DOS
- (D) SOFTWARE: PatentIn Release #1.0, Version #1.30 (EPO)

(2) INFORMATION FOR SEQ ID NO: 1:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 15 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 1:

Met	Ala	Lys	Thr	Ile	Ala	Tyr	Asp	Glu	Glu	Ala	Arg	Arg	Gly	Leu
1				5				10					15	

(2) INFORMATION FOR SEQ ID NO: 2:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 17 amino acids
- (B) TYPE: amino acid

- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 2:

Ala Tyr Asp Glu Glu Ala Arg Arg Gly Leu Glu Arg Gly Leu Asn Ser
1 5 10 15
Leu

(2) INFORMATION FOR SEQ ID NO: 3:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 17 amino acids
 - (B) TYPE: amino acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 3:

Ala Arg Arg Gly Leu Glu Arg Gly Leu Asn Ser Leu Ala Asp Ala Val
1 5 10 15
Lys

(2) INFORMATION FOR SEQ ID NO: 4:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 19 amino acids
 - (B) TYPE: amino acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 4:

Glu Arg Gly Leu Asn Ser Leu Ala Asp Ala Val Lys Val Thr Leu Gly
1 5 10 15

Pro Lys Gly

(2) INFORMATION FOR SEQ ID NO: 5:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 17 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 5:

Ser Leu Ala Asp Ala Val Lys Val Thr Leu Gly Pro Lys Gly Arg Asn
1 5 10 15

Val

(2) INFORMATION FOR SEQ ID NO: 6:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 16 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 6:

Val Lys Val Thr Leu Gly Pro Lys Gly Arg Asn Val Val Leu Glu Lys
1 5 10 15

(2) INFORMATION FOR SEQ ID NO: 7:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 15 amino acids
(B) TYPE: amino acid

- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 7:

Gly	Pro	Lys	Gly	Arg	Asn	Val	Val	Leu	Glu	Lys	Lys	Trp	Gly	Ala
1				5				10					15	

(2) INFORMATION FOR SEQ ID NO: 8:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 16 amino acids
 - (B) TYPE: amino acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 8:

Asn	Val	Val	Leu	Glu	Lys	Lys	Trp	Gly	Ala	Pro	Thr	Ile	Thr	Asn	Asp
1				5				10						15	

(2) INFORMATION FOR SEQ ID NO: 9:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 15 amino acids
 - (B) TYPE: amino acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 9:

Lys	Lys	Trp	Gly	Ala	Pro	Thr	Ile	Thr	Asn	Asp	Gly	Val	Ser	Ile
1				5				10						15

(2) INFORMATION FOR SEQ ID NO: 10:

- (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 16 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 10:

Pro	Thr	Ile	Thr	Asn	Asp	Gly	Val	Ser	Ile	Ala	Lys	Glu	Ile	Glu	Leu
1				5					10					15	

(2) INFORMATION FOR SEQ ID NO: 11:

- (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 17 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 11:

Asp	Gly	Tyr	Ser	Ile	Ala	Lys	Glu	Ile	Glu	Leu	Glu	Asp	Pro	Tyr	Glu
1				5					10					15	

Lys

(2) INFORMATION FOR SEQ ID NO: 12:

- (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 19 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 12:

Ala Lys Glu Ile Glu Leu Glu Asp Pro Tyr Glu Lys Ile Gly Ala Glu
1 5 10 15

Leu Val Lys

(2) INFORMATION FOR SEQ ID NO: 13:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 18 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 13:

Leu Glu Asp Pro Tyr Glu Lys Ile Gly Ala Glu Leu Val Lys Glu Val
1 5 10 15

Ala Lys

(2) INFORMATION FOR SEQ ID NO: 14:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 19 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 14:

Glu Lys Ile Gly Ala Glu Leu Val Lys Glu Val Ala Lys Lys Thr Asp
1 5 10 15

Asp Val Ala

(2) INFORMATION FOR SEQ ID NO: 15:

- (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 16 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 15:

Glu	Leu	Val	Lys	Glu	Val	Ala	Lys	Lys	Thr	Asp	Asp	Val	Ala	Gly	Asp
1				5					10					15	

(2) INFORMATION FOR SEQ ID NO: 16:

- (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 19 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 16:

Val	Ala	Lys	Lys	Thr	Asp	Asp	Val	Ala	Gly	Asp	Gly	Thr	Thr	Thr	Ala
1				5					10					15	

Thr Val Leu

(2) INFORMATION FOR SEQ ID NO: 17:

- (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 19 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 17:

Asp Asp Val Ala Gly Asp Gly Thr Thr Thr Ala Thr Val Leu Ala Gln
 1 5 10 15

Ala Leu Val

(2) INFORMATION FOR SEQ ID NO: 18:

- (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 18 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 18:

Asp Gly Thr Thr Thr Ala Thr Val Leu Ala Gln Ala Leu Val Lys Glu
 1 5 10 15

Gly Leu

(2) INFORMATION FOR SEQ ID NO: 19:

- (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 19 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 19:

Gln Ala Leu Val Lys Glu Gly Leu Arg Asn Val Ala Ala Gly Ala Asn
 1 5 10 15

Pro Leu Gly

(2) INFORMATION FOR SEQ ID NO: 20:

- (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 18 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 20:

Glu Gly Leu Arg Asn Val Ala Ala Gly Ala Asn Pro Leu Gly Leu Lys
1 5 10 15

Arg Gly

(2) INFORMATION FOR SEQ ID NO: 21:

- (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 17 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 21:

Val Ala Ala Gly Ala Asn Pro Leu Gly Leu Lys Arg Gly Ile Glu Lys
1 5 10 15

Ala

(2) INFORMATION FOR SEQ ID NO: 22:

- (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 16 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 22:

Asn	Pro	Leu	Gly	Leu	Lys	Arg	Gly	Ile	Glu	Lys	Ala	Val	Asp	Lys	Val
1				5					10					15	

(2) INFORMATION FOR SEQ ID NO: 23:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 15 amino acids
 - (B) TYPE: amino acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 23:

Lys	Arg	Gly	Ile	Glu	Lys	Ala	Val	Asp	Lys	Val	Thr	Glu	Thr	Leu
1				5					10					15

(2) INFORMATION FOR SEQ ID NO: 24:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 15 amino acids
 - (B) TYPE: amino acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 24:

Lys	Ala	Val	Asp	Lys	Val	Thr	Glu	Thr	Leu	Leu	Lys	Asp	Ala	Lys
1				5					10					15

(2) INFORMATION FOR SEQ ID NO: 25:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 15 amino acids
 - (B) TYPE: amino acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 25:

Val	Thr	Glu	Thr	Leu	Leu	Lys	Asp	Ala	Lys	Glu	Val	Glu	Thr	Lys
1				5					10					15

(2) INFORMATION FOR SEQ ID NO: 26:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 15 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 26:

Leu	Lys	Asp	Ala	Lys	Glu	Val	Glu	Thr	Lys	Glu	Gln	Ile	Ala	Ala
1				5					10					15

(2) INFORMATION FOR SEQ ID NO: 27:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 16 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 27:

Glu	Val	Glu	Thr	Lys	Glu	Gln	Ile	Ala	Ala	Thr	Ala	Ala	Ile	Ser	Ala
1				5					10					15	

(2) INFORMATION FOR SEQ ID NO: 28:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 17 amino acids

- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 28:

Gln	Ile	Ala	Ala	Thr	Ala	Ala	Ile	Ser	Ala	Gly	Asp	Gln	Ser	Ile	Gly
1				5				10						15	

Asp

(2) INFORMATION FOR SEQ ID NO: 29:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 15 amino acids
 - (B) TYPE: amino acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 29:

Thr	Ala	Ala	Ile	Ser	Ala	Gly	Asp	Gln	Ser	Ile	Gly	Asp	Leu	Ile
1				5				10					15	

(2) INFORMATION FOR SEQ ID NO: 30:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 18 amino acids
 - (B) TYPE: amino acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 30:

Ala Gly Asp Gln Ser Ile Gly Asp Leu Ile Ala Glu Ala Met Asp Lys

1	5	10	15
Val	Gly		

(2) INFORMATION FOR SEQ ID NO: 31:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 16 amino acids
 - (B) TYPE: amino acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 31:

Ile	Gly	Asp	Leu	Ile	Ala	Glu	Ala	Met	Asp	Lys	Val	Gly	Asn	Glu	Gly
1				5					10					15	

(2) INFORMATION FOR SEQ ID NO: 32:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 15 amino acids
 - (B) TYPE: amino acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 32:

Ala	Glu	Ala	Met	Asp	Lys	Val	Gly	Asn	Glu	Gly	Val	Ile	Thr	Val
1				5				10					15	

(2) INFORMATION FOR SEQ ID NO: 33:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 18 amino acids
 - (B) TYPE: amino acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 33:

Lys val Gly Asn Glu Gly Val Ile Thr val Glu Glu Ser Asn Thr Phe
1 5 10 15

Gly Leu

(2) INFORMATION FOR SEQ ID NO: 34:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 15 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 34:

Gly Val Ile Thr Val Glu Glu Ser Asn Thr Phe Gly Leu Gln Leu
1 5 10 15

(2) INFORMATION FOR SEQ ID NO: 35:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 15 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 35:

Glu Glu Ser Asn Thr Phe Gly Leu Gln Leu Glu Leu Thr Glu Gly
1 5 10 15

(2) INFORMATION FOR SEQ ID NO: 36:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 16 amino acids

41

- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 36:

Phe	Gly	Leu	Gln	Leu	Glu	Leu	Thr	Glu	Gly	Met	Arg	Phe	Asp	Lys	Gly
1			5					10						15	

(2) INFORMATION FOR SEQ ID NO: 37:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 15 amino acids
 - (B) TYPE: amino acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 37:

Glu	Leu	Thr	Glu	Gly	Met	Arg	Phe	Asp	Lys	Gly	Tyr	Ile	Ser	Gly
1			5					10						15

(2) INFORMATION FOR SEQ ID NO: 38:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 16 amino acids
 - (B) TYPE: amino acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 38:

Met	Arg	Phe	Asp	Lys	Gly	Tyr	Ile	Ser	Gly	Tyr	Phe	Val	Thr	Asp	Ala
1				5					10					15	

(2) INFORMATION FOR SEQ ID NO: 39:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 16 amino acids
 - (B) TYPE: amino acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 39:

Gly	Tyr	Ile	Ser	Gly	Tyr	Phe	Val	Thr	Asp	Ala	Glu	Arg	Gln	Glu	Ala
1				5					10					15	

(2) INFORMATION FOR SEQ ID NO: 40:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 18 amino acids
 - (B) TYPE: amino acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 40:

Tyr	Phe	Val	Thr	Asp	Ala	Glu	Arg	Gln	Glu	Ala	Val	Leu	Glu	Glu	Pro
1				5				10					15		

Tyr Ile

(2) INFORMATION FOR SEQ ID NO: 41:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 15 amino acids
 - (B) TYPE: amino acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 41:

Ala	Glu	Arg	Gln	Glu	Ala	Val	Leu	Glu	Glu	Pro	Tyr	Ile	Leu	Leu
1				5					10					15

(2) INFORMATION FOR SEQ ID NO: 42:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 19 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 42:

Ala	Val	Leu	Glu	Glu	Pro	Tyr	Ile	Leu	Leu	Val	Ser	Ser	Lys	Val	Ser
1				5					10					15	

Thr Val Lys

(2) INFORMATION FOR SEQ ID NO: 43:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 15 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 43:

Pro	Tyr	Ile	Leu	Leu	Val	Ser	Ser	Lys	Val	Ser	Thr	Val	Lys	Asp
1				5					10					15

(2) INFORMATION FOR SEQ ID NO: 44:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 18 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single

44

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 44:

Val	Ser	Ser	Lys	Val	Ser	Thr	Val	Lys	Asp	Leu	Leu	Pro	Leu	Leu	Glu
1			5					10					15		

Lys Val

(2) INFORMATION FOR SEQ ID NO: 45:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 18 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 45:

Ser	Thr	Val	Lys	Asp	Leu	Leu	Pro	Leu	Leu	Glu	Lys	Val	Ile	Gln	Ala
1			5					10					15		

Gly Lys

(2) INFORMATION FOR SEQ ID NO: 46:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 19 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 46:

45

Leu Leu Pro Leu Leu Glu Lys Val Ile Gln Ala Gly Lys Ser Leu Leu
1 5 10 15

Ile Ile Ala

(2) INFORMATION FOR SEQ ID NO: 47:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 16 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 47:

Glu Lys Val Ile Gln Ala Gly Lys Ser Leu Leu Ile Ile Ala Glu Asp
1 5 10 15

(2) INFORMATION FOR SEQ ID NO: 48:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 17 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 48:

Ala Gly Lys Ser Leu Leu Ile Ile Ala Glu Asp Val Glu Gly Glu Ala
1 5 10 15

Leu

(2) INFORMATION FOR SEQ ID NO: 49:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 15 amino acids
- (B) TYPE: amino acid

- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 49:

Leu	Ile	Ile	Ala	Glu	Asp	Val	Glu	Gly	Glu	Ala	Leu	Ser	Thr	Leu
1				5				10						15

(2) INFORMATION FOR SEQ ID NO: 50:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 17 amino acids
 - (B) TYPE: amino acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 50:

Asp	Val	Glu	Gly	Glu	Ala	Leu	Ser	Thr	Leu	Val	Val	Asn	Lys	Ile	Arg
1				5					10					15	

Gly

(2) INFORMATION FOR SEQ ID NO: 51:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 16 amino acids
 - (B) TYPE: amino acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 51:

Val	Val	Asn	Lys	Ile	Arg	Gly	Thr	Phe	Lys	Ser	Val	Ala	Val	Lys	Ala
1				5					10					15	

(2) INFORMATION FOR SEQ ID NO: 52:

- (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 16 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 52:

Arg	Gly	Thr	Phe	Lys	Ser	Val	Ala	Val	Lys	Ala	Pro	Gly	Phe	Gly	Asp
1				5					10					15	

(2) INFORMATION FOR SEQ ID NO: 53:

- (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 19 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 53:

Ser	Val	Ala	Val	Lys	Ala	Pro	Gly	Phe	Gly	Asp	Arg	Arg	Lys	Ala	Met
1				5					10					15	

Leu Gln Asp

(2) INFORMATION FOR SEQ ID NO: 54:

- (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 17 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 54:

Ala Pro Gly Phe Gly Asp Arg Arg Lys Ala Met Leu Gln Asp Met Ala
1 5 10 15

Ile

(2) INFORMATION FOR SEQ ID NO: 55:

- (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 18 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 55:

Asp Arg Arg Lys Ala Met Leu Gln Asp Met Ala Ile Leu Thr Gly Ala
1 5 10 15

Gln Val

(2) INFORMATION FOR SEQ ID NO: 56:

- (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 19 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 56:

Met Leu Gln Asp Met Ala Ile Leu Thr Gly Ala Gln Val Ile Ser Glu
1 5 10 15

Glu Val Gly

(2) INFORMATION FOR SEQ ID NO: 57:

- (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 15 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 57:

Ala	Ile	Leu	Thr	Gly	Ala	Gln	Val	Ile	Ser	Glu	Glu	Val	Gly	Leu
1				5					10					15

(2) INFORMATION FOR SEQ ID NO: 58:

- (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 17 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 58:

Ala	Gln	Val	Ile	Ser	Glu	Glu	Val	Gly	Leu	Thr	Leu	Glu	Asn	Thr	Asp
1				5				10					15		

Leu

(2) INFORMATION FOR SEQ ID NO: 59:

- (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 15 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

50

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 59:

Glu	Glu	Val	Gly	Leu	Thr	Leu	Glu	Asn	Thr	Asp	Leu	Ser	Leu	Leu
1				5					10				15	

(2) INFORMATION FOR SEQ ID NO: 60:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 15 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 60:

Thr	Leu	Glu	Asn	Thr	Asp	Leu	Ser	Leu	Leu	Gly	Lys	Ala	Arg	Lys
1				5					10					15

(2) INFORMATION FOR SEQ ID NO: 61:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 15 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 61:

Asp	Leu	Ser	Leu	Leu	Gly	Lys	Ala	Arg	Lys	Val	Val	Met	Thr	Lys
1				5					10					15

(2) INFORMATION FOR SEQ ID NO: 62:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 18 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 62:

Gly	Lys	Ala	Arg	Lys	Val	Val	Met	Thr	Lys	Asp	Glu	Thr	Thr	Ile	Val
1				5					10					15	

Glu Gly

(2) INFORMATION FOR SEQ ID NO: 63:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 15 amino acids
 - (B) TYPE: amino acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 63:

Val	Val	Met	Thr	Lys	Asp	Glu	Thr	Thr	Ile	Val	Glu	Gly	Ala	Gly
1				5					10					15

(2) INFORMATION FOR SEQ ID NO: 64:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 17 amino acids
 - (B) TYPE: amino acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 64:

Asp	Glu	Thr	Thr	Ile	Val	Glu	Gly	Ala	Gly	Asp	Thr	Asp	Ala	Ile	Ala
1				5					10					15	

Gly

(2) INFORMATION FOR SEQ ID NO: 65:

52

- (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 15 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 65:

Val	Glu	Gly	Ala	Gly	Asp	Thr	Asp	Ala	Ile	Ala	Gly	Arg	Val	Ala
1				5					10				15	

(2) INFORMATION FOR SEQ ID NO: 66:

- (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 16 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 66:

Asp	Thr	Asp	Ala	Ile	Ala	Gly	Arg	Val	Ala	Gln	Ile	Arg	Thr	Glu	Ile
1				5					10					15	

(2) INFORMATION FOR SEQ ID NO: 67:

- (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 15 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 67:

Ala Gly Arg Val Ala Gln Ile Arg Thr Glu Ile Glu Asn Ser Asp

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 70:

Ser	Asp	Tyr	Asp	Arg	Glu	Lys	Leu	Gln	Glu	Arg	Leu	Ala	Lys	Leu
1				5				10					15	

(2) INFORMATION FOR SEQ ID NO: 71:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 18 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 71:

Glu	Lys	Leu	Gln	Glu	Arg	Leu	Ala	Lys	Leu	Ala	Gly	Gly	Val	Ala	Val
1				5				10					15		

Ile Lys

(2) INFORMATION FOR SEQ ID NO: 72:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 15 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 72:

Arg	Leu	Ala	Lys	Leu	Ala	Gly	Gly	Val	Ala	Val	Ile	Lys	Ala	Gly
1				5				10					15	

(2) INFORMATION FOR SEQ ID NO: 73:

55

- (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 15 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 73:

Ala	Gly	Gly	Val	Ala	Val	Ile	Lys	Ala	Gly	Ala	Ala	Thr	Glu	Val
1				5				10						15

(2) INFORMATION FOR SEQ ID NO: 74:

- (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 19 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 74:

Val	Ile	Lys	Ala	Gly	Ala	Ala	Thr	Glu	Val	Glu	Leu	Lys	Glu	Arg	Lys
1				5				10						15	

His Arg Ile

(2) INFORMATION FOR SEQ ID NO: 75:

- (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 17 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 75:

56

Ala Ala Thr Glu Val Glu Leu Lys Glu Arg Lys His Arg Ile Glu Asp
1 5 10 15

Ala

(2) INFORMATION FOR SEQ ID NO: 76:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 17 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 76:

Glu Leu Lys Glu Arg Lys His Arg Ile Glu Asp Ala Val Arg Asn Ala
1 5 10 15

Lys

(2) INFORMATION FOR SEQ ID NO: 77:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 18 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 77:

Lys His Arg Ile Glu Asp Ala Val Arg Asn Ala Lys Ala Ala Val Glu
1 5 10 15

Glu Gly

(2) INFORMATION FOR SEQ ID NO: 78:

(i) SEQUENCE CHARACTERISTICS:

57

- (A) LENGTH: 17 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 78:

Asp Ala Val Arg Asn Ala Lys Ala Ala Val Glu Glu Gly Ile Val Ala
1 5 10 15
Gly

(2) INFORMATION FOR SEQ ID NO: 79:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 15 amino acids
 - (B) TYPE: amino acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 79:

Ala Lys Ala Ala Val Glu Glu Gly Ile Val Ala Gly Gly Gly Val
1 5 10 15

(2) INFORMATION FOR SEQ ID NO: 80:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 19 amino acids
 - (B) TYPE: amino acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 80:

58

Glu Glu Gly Ile Val Ala Gly Gly Gly Val Thr Leu Leu Gln Ala Ala
1 5 10 15

Pro Ala Leu

(2) INFORMATION FOR SEQ ID NO: 81:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 17 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 81:

Ala Gly Gly Gly Val Thr Leu Leu Gln Ala Ala Pro Ala Leu Asp Lys
1 5 10 15

Leu

(2) INFORMATION FOR SEQ ID NO: 82:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 16 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 82:

Thr Leu Leu Gln Ala Ala Pro Ala Leu Asp Lys Leu Lys Leu Thr Gly
1 5 10 15

(2) INFORMATION FOR SEQ ID NO: 83:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 16 amino acids
(B) TYPE: amino acid

(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 83:

Ala	Pro	Ala	Leu	Asp	Lys	Leu	Lys	Leu	Thr	Gly	Asp	Glu	Ala	Thr	Gly
1				5					10					15	

(2) INFORMATION FOR SEQ ID NO: 84:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 18 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 84:

Lys	Leu	Lys	Leu	Thr	Gly	Asp	Glu	Ala	Thr	Gly	Ala	Asn	Ile	Val	Lys
1				5					10					15	

Val Ala

(2) INFORMATION FOR SEQ ID NO: 85:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 16 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 85:

Gly Asp Glu Ala Thr Gly Ala Asn Ile Val Lys Val Ala Leu Glu Ala

1

5

10

15

(2) INFORMATION FOR SEQ ID NO: 86:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 17 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 86:

Gly Ala Asn Ile Val Lys Val Ala Leu Glu Ala Pro Leu Lys Gln Ile
1 5 10 15
Ala

(2) INFORMATION FOR SEQ ID NO: 87:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 16 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 87:

Lys Val Ala Leu Glu Ala Pro Leu Lys Gln Ile Ala Phe Asn Ser Gly
1 5 10 15

(2) INFORMATION FOR SEQ ID NO: 88:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 16 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 88:

Ala	Pro	Leu	Lys	Gln	Ile	Ala	Phe	Asn	Ser	Gly	Met	Glu	Pro	Gly	Val
1				5					10					15	

(2) INFORMATION FOR SEQ ID NO: 89:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 16 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 89:

Ile	Ala	Phe	Asn	Ser	Gly	Met	Glu	Pro	Gly	Val	Val	Ala	Glu	Lys	Val
1				5					10					15	

(2) INFORMATION FOR SEQ ID NO: 90:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 16 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 90:

Gly	Met	Glu	Pro	Gly	Val	Val	Ala	Glu	Lys	Val	Arg	Asn	Leu	Ser	Val
1				5					10					15	

(2) INFORMATION FOR SEQ ID NO: 91:

62

- (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 91:

Val	Val	Ala	Glu	Lys	Val	Arg	Asn	Leu	Ser	Val	Gly	His	Gly	Leu
1				5					10					15

(2) INFORMATION FOR SEQ ID NO: 92:

- (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 92:

Val	Arg	Asn	Leu	Ser	Val	Gly	His	Gly	Leu	Asn	Ala	Ala	Thr	Gly
1				5					10					15

(2) INFORMATION FOR SEQ ID NO: 93:

- (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 93:

Val	Gly	His	Gly	Leu	Asn	Ala	Ala	Thr	Gly	Glu	Tyr	Glu	Asp	Leu
1				5					10					15

(2) INFORMATION FOR SEQ ID NO: 94:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 16 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 94:

Asn	Ala	Ala	Thr	Gly	Glu	Tyr	Glu	Asp	Leu	Leu	Lys	Ala	Gly	Val	Ala
1				5					10					15	

(2) INFORMATION FOR SEQ ID NO: 95:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 16 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 95:

Glu	Tyr	Glu	Asp	Leu	Leu	Lys	Ala	Gly	Val	Ala	Asp	Pro	Val	Lys	Val
1				5					10					15	

(2) INFORMATION FOR SEQ ID NO: 96:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 16 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

64

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 96:

Leu Lys Ala Gly Val Ala Asp Pro Val Lys Val Thr Arg Ser Ala Leu
1 5 10 15

(2) INFORMATION FOR SEQ ID NO: 97:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 19 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 97:

Ala Asp Pro Val Lys Val Thr Arg Ser Ala Leu Gln Asn Ala Ala Ser
1 5 10 15

Ile Ala Gly

(2) INFORMATION FOR SEQ ID NO: 98:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 15 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 98:

Val Thr Arg Ser Ala Leu Gln Asn Ala Ala Ser Ile Ala Gly Leu
1 5 10 15

(2) INFORMATION FOR SEQ ID NO: 99:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 16 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 99:

Leu	Gln	Asn	Ala	Ala	Ser	Ile	Ala	Gly	Leu	Phe	Leu	Thr	Thr	Glu	Ala
1				5				10						15	

(2) INFORMATION FOR SEQ ID NO: 100:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 15 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 100:

Ser	Ile	Ala	Gly	Leu	Phe	Leu	Thr	Thr	Glu	Ala	Val	Val	Ala	Asp
1				5				10					15	

(2) INFORMATION FOR SEQ ID NO: 101:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 16 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 101:

Phe	Leu	Thr	Thr	Glu	Ala	Val	Val	Ala	Asp	Lys	Pro	Glu	Lys	Thr	Ala
1				5				10						15	

(2) INFORMATION FOR SEQ ID NO: 102:

- (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 16 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 102:

Ala	Val	Val	Ala	Asp	Lys	Pro	Glu	Lys	Thr	Ala	Ala	Pro	Ala	Ser	Asp
1				5					10					15	

(2) INFORMATION FOR SEQ ID NO: 103:

- (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 15 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 103:

Lys	Pro	Glu	Lys	Thr	Ala	Ala	Pro	Ala	Ser	Asp	Pro	Thr	Gly	Gly
1				5					10					15

(2) INFORMATION FOR SEQ ID NO: 104:

- (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 16 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 104:

Ala Ala Pro Ala Ser Asp Pro Thr Gly Gly Met Gly Gly Met Asp Phe

1

5

10

15

(2) INFORMATION FOR SEQ ID NO: 105:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 573 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 105:

Met	Leu	Arg	Leu	Pro	Thr	Val	Phe	Arg	Gln	Met	Arg	Pro	Val	Ser	Arg	1	5	10	15
Val	Leu	Ala	Pro	His	Leu	Thr	Arg	Ala	Tyr	Ala	Lys	Asp	Val	Lys	Phe	20	25	30	
Gly	Ala	Asp	Ala	Arg	Ala	Leu	Met	Leu	Gln	Gly	Val	Asp	Leu	Leu	Ala	35	40	45	
Asp	Ala	Val	Ala	Val	Thr	Met	Gly	Pro	Lys	Gly	Arg	Thr	Val	Ile	Ile	50	55	60	
Glu	Gln	Ser	Trp	Gly	Ser	Pro	Lys	Val	Thr	Lys	Asp	Gly	Val	Thr	Val	65	70	75	80
Ala	Lys	Ser	Ile	Asp	Leu	Lys	Asp	Lys	Tyr	Arg	Asn	Ile	Gly	Ala	Lys	85	90	95	
Leu	Val	Gln	Asp	Val	Ala	Asn	Asn	Thr	Asn	Glu	Glu	Ala	Gly	Asp	Gly	100	105	110	
Thr	Thr	Thr	Ala	Thr	Val	Leu	Ala	Arg	Ser	Ile	Ala	Lys	Glu	Gly	Phe	115	120	125	
Glu	Lys	Ile	Ser	Lys	Gly	Ala	Asn	Pro	Val	Glu	Ile	Arg	Arg	Gly	Val	130	135	140	
Met	Leu	Ala	Val	Asp	Ala	Val	Ile	Ala	Glu	Leu	Lys	Lys	Gln	Ser	Lys	145	150	155	160
Pro	Val	Thr	Thr	Pro	Glu	Glu	Ile	Ala	Gln	Val	Ala	Thr	Ile	Ser	Ala	165	170	175	

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Asn Gly Asp Lys Glu Ile Gly Asn Ile Ile Ser Asp Ala Met Lys Lys
 180 185 190

Val Gly Arg Lys Gly Val Ile Thr Val Lys Asp Gly Lys Thr Leu Asn
 195 200 205

Asp Glu Leu Glu Ile Ile Glu Gly Met Lys Phe Asp Arg Gly Tyr Ile
 210 215 220

Ser Pro Tyr Phe Ile Asn Thr Ser Lys Gly Gln Lys Cys Glu Phe Gln
 225 230 235 240

Asp Ala Tyr Val Leu Leu Ser Glu Lys Lys Ile Ser Ser Ile Gln Ser
 245 250 255

Ile Val Pro Ala Leu Glu Ile Ala Asn Ala His Arg Lys Pro Leu Val
 260 265 270

Ile Ile Ala Glu Asp Val Asp Gly Glu Ala Leu Ser Thr Leu Val Leu
 275 280 285

Asn Arg Leu Lys Val Gly Leu Gln Val Val Ala Val Lys Ala Pro Gly
 290 295 300

Phe Gly Asp Asn Arg Lys Asn Gln Leu Lys Asp Met Ala Ile Ala Thr
 305 310 315 320

Gly Gly Ala Val Phe Gly Glu Glu Gly Leu Thr Leu Asn Leu Glu Asp
 325 330 335

Val Gln Pro His Asp Leu Gly Lys Val Gly Glu Val Ile Val Thr Lys
 340 345 350

Asp Asp Ala Met Leu Leu Lys Gly Lys Gly Asp Lys Ala Gln Ile Glu
 355 360 365

Lys Arg Ile Gln Glu Ile Ile Glu Gln Leu Asp Val Thr Thr Ser Glu
 370 375 380

Val Glu Lys Glu Lys Leu Asn Glu Arg Leu Ala Lys Leu Ser Asp Gly
 385 390 395 400

Val Ala Val Leu Lys Val Gly Gly Thr Ser Asp Val Glu Val Asn Glu
 405 410 415

Lys Lys Asp Arg Val Thr Asp Ala Leu Asn Ala Thr Arg Ala Ala Val
 420 425 430

Glu Glu Gly Ile Val Leu Gly Gly Gly Cys Ala Leu Leu Arg Cys Ile
 435 440 445

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Pro	Ala	Leu	Asp	Ser	Leu	Thr	Pro	Ala	Asn	Glu	Asp	Gln	Lys	Ile	Gly
450						455					460				
Ile	Glu	Ile	Ile	Lys	Arg	Thr	Leu	Lys	Ile	Pro	Ala	Met	Thr	Ile	Ala
465					470					475					480
Lys	Asn	Ala	Gly	Val	Glu	Gly	Ser	Leu	Ile	Val	Glu	Lys	Ile	Met	Gln
				485					490					495	
Ser	Ser	Ser	Glu	Val	Gly	Tyr	Asp	Ala	Met	Ala	Gly	Asp	Phe	Val	Asn
			500					505					510		
Met	Val	Glu	Lys	Gly	Ile	Ile	Asp	Pro	Thr	Lys	Val	Val	Arg	Thr	Ala
		515					520					525			
Leu	Leu	Asp	Ala	Ala	Gly	Val	Ala	Ser	Leu	Leu	Thr	Thr	Ala	Glu	Val
		530				535					540				
Val	Val	Thr	Glu	Ile	Pro	Lys	Glu	Glu	Lys	Asp	Pro	Gly	Met	Gly	Ala
545					550					555					560
Met	Gly	Gly	Met	Gly	Gly	Gly	Met	Gly	Gly	Gly	Met	Phe			
				565					570						

(2) INFORMATION FOR SEQ ID NO: 106:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 544 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 106:

Met	Ala	Lys	Thr	Ile	Ala	Tyr	Asp	Glu	Glu	Ala	Arg	Arg	Gly	Leu	Glu
1				5					10					15	
Arg	Gly	Leu	Asn	Ala	Leu	Ala	Asp	Ala	Val	Lys	Val	Thr	Leu	Gly	Pro
			20					25					30		
Lys	Gly	Arg	Asn	Val	Val	Leu	Glu	Lys	Lys	Trp	Gly	Ala	Pro	Thr	Ile
		35					40					45			
Thr	Asn	Asp	Gly	Val	Ser	Ile	Ala	Lys	Glu	Ile	Glu	Leu	Glu	Asp	Pro
		50				55					60				

70

Tyr Glu Lys Ile Gly Ala Glu Leu Val Lys Glu Val Ala Lys Lys Thr
 65 70 75 80

Asp Asp Val Ala Gly Asp Gly Thr Thr Thr Ala Thr Val Leu Ala Gln
 85 90 95

Ala Leu Val Arg Glu Gly Leu Arg Asn Val Ala Ala Gly Ala Asn Pro
 100 105 110

Leu Gly Leu Lys Arg Gly Ile Glu Lys Ala Val Glu Lys Val Thr Glu
 115 120 125

Thr Leu Ile Lys Gly Ala Lys Glu Val Glu Thr Lys Glu Gln Ile Ala
 130 135 140

Ala Thr Ala Ala Ile Ser Ala Gly Asp Gln Ser Ile Gly Asp Ser Ile
 145 150 155 160

Gly Asp Leu Ile Ala Glu Ala Met Asp Lys Val Gly Asn Glu Gly Val
 165 170 175

Ile Thr Val Glu Glu Ser Asn Thr Phe Gly Leu Gln Leu Glu Ile Thr
 180 185 190

Glu Gly Met Arg Phe Asp Lys Gly Tyr Ile Ser Gly Tyr Phe Val Thr
 195 200 205

Asp Pro Glu Arg Gln Glu Ala Val Leu Glu Asp Pro Tyr Ile Leu Leu
 210 215 220

Val Ser Ser Lys Val Ser Thr Val Lys Asp Leu Leu Pro Leu Leu Glu
 225 230 235 240

Lys Val Ile Gly Ala Gly Lys Pro Leu Leu Ile Ile Ala Glu Asp Val
 245 250 255

Glu Gly Glu Ala Leu Ser Thr Leu Val Val Asn Lys Ile Arg Gly Thr
 260 265 270

Phe Lys Ser Val Ala Val Lys Ala Pro Gly Phe Gly Asp Arg Arg Lys
 275 280 285

Ala Met Leu Gln Asp Met Ala Ile Leu Thr Gly Gly Gln Val Ile Ser
 290 295 300

Glu Glu Val Gly Leu Thr Leu Glu Asn Ala Asp Leu Ser Leu Leu Gly
 305 310 315 320

Lys Ala Arg Lys Val Val Val Thr Lys Asp Glu Thr Thr Ile Val Glu
 325 330 335

Gly	Ala	Gly	Asp	Thr	Asp	Ala	Ile	Ala	Gly	Arg	Val	Ala	Gln	Ile	Arg	340	345	350	
Gln	Glu	Ile	Glu	Asn	Ser	Asp	Ser	Asp	Tyr	Asp	Arg	Glu	Lys	Leu	Gln	355	360	365	
Glu	Arg	Leu	Ala	Lys	Leu	Ala	Gly	Gly	Val	Ala	Val	Ile	Lys	Ala	Gly	370	375	380	
Ala	Ala	Thr	Glu	Val	Glu	Leu	Lys	Glu	Arg	Lys	His	Arg	Ile	Glu	Asp	385	390	395	400
Ala	Val	Arg	Asn	Ala	Lys	Ala	Ala	Val	Glu	Glu	Gly	Ile	Val	Ala	Gly	405	410	415	
Gly	Gly	Val	Thr	Leu	Leu	Gln	Ala	Ala	Pro	Thr	Leu	Asp	Ala	Leu	Lys	420	425	430	
Leu	Glu	Gly	Asp	Glu	Ala	Thr	Gly	Ala	Asn	Ile	Val	Lys	Val	Ala	Leu	435	440	445	
Glu	Ala	Pro	Leu	Lys	Gly	Ile	Ala	Phe	Asn	Ser	Gly	Leu	Glu	Pro	Gly	450	455	460	
Val	Val	Ala	Glu	Lys	Val	Arg	Asn	Leu	Pro	Ala	Gly	His	Gly	Leu	Asn	465	470	475	480
Ala	Gln	Thr	Gly	Val	Tyr	Glu	Asp	Leu	Leu	Ala	Ala	Gly	Val	Ala	Asp	485	490	495	
Pro	Val	Lys	Val	Thr	Arg	Ser	Ala	Leu	Gln	Asn	Ala	Ala	Ser	Ile	Ala	500	505	510	
Gly	Leu	Phe	Leu	Thr	Thr	Glu	Ala	Val	Val	Ala	Asp	Lys	Pro	Glu	Lys	515	520	525	
Glu	Lys	Ala	Ser	Val	Pro	Gly	Gly	Gly	Asp	Met	Gly	Gly	Met	Asp	Phe	530	535	540	

(2) INFORMATION FOR SEQ ID NO: 107:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 17 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 107:

Thr Ala Ala Pro Ala Ser Asp Pro Thr Gly Gly Met Gly Gly Met Asp
1 5 10 15

Phe

(2) INFORMATION FOR SEQ ID NO: 108:

- (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 11 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 108:

Asp Val Glu Gly Glu Ala Leu Ser Thr Leu Val
1 5 10

(2) INFORMATION FOR SEQ ID NO: 109:

- (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 11 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 109:

Asp Val Asp Gly Glu Ala Leu Ser Thr Leu Val
1 5 10

(2) INFORMATION FOR SEQ ID NO: 110:

- (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 11 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 110:

Val	Val	Asn	Lys	Ile	Arg	Gly	Thr	Phe	Lys	Ser
1				5					10	

(2) INFORMATION FOR SEQ ID NO: 111:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 16 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 111:

Phe	Leu	Thr	Thr	Glu	Ala	Val	Val	Ala	Asp	Lys	Pro	Glu	Lys	Thr	Ala
1				5					10					15	

(2) INFORMATION FOR SEQ ID NO: 112:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 10 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 112:

Val	Ala	Val	Lys	Ala	Pro	Gly	Phe	Gly	Asp
1				5					10

(2) INFORMATION FOR SEQ ID NO: 113:

- (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 113:

Arg	Arg	Lys	Ala	Met	Leu	Gln	Asp	Met	Ala	Ile	Leu	Thr	Gly	Gly
1				5				10					15	

(2) INFORMATION FOR SEQ ID NO: 114:

- (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 12 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 114:

Val	Gly	Leu	Thr	Leu	Glu	Asn	Ala	Asp	Leu	Ser	Leu
1				5				10			

(2) INFORMATION FOR SEQ ID NO: 115:

- (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 12 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 115:

Leu	Thr	Leu	Asn	Leu	Glu	Asp	Val	Gln	Pro	His	Asp
1				5				10			

(2) INFORMATION FOR SEQ ID NO: 116:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 12 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 116:

Val Gly Leu Thr Leu Glu Asn Ala Asp Leu Ser Leu
1 5 10

(2) INFORMATION FOR SEQ ID NO: 117:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 12 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 117:

Leu Thr Leu Asn Leu Glu Asp Val Gln Pro His Asp
1 5 10

Claims

1. A polypeptide of up to 21 amino acid residues which comprises or consists of the sequence

VGLTLENADLSL (SEQ ID 107)

or a homologue or functional equivalent or mimetic thereof.

2. The polypeptide of claim 1 for use in prophylaxis or treatment of auto-immune disease such as rheumatoid arthritis.

3. A polypeptide of up to 21 amino acid residues comprising or consisting of the sequence

VLNRLKVGLQV (SEQ ID 108)

or a homologue or functional equivalent or mimetic thereof.

4. Human hsp58 polypeptide or a fragment thereof containing or consisting of the amino acid sequence of claim 3 for use in the prophylaxis or treatment of auto-immune disease such as rheumatoid arthritis.

5. A polypeptide of up to 21 amino acid residues comprising or consisting of the sequence

LTLNLEDVQPHD (SEQ ID 110)

or a homologue or functional equivalent or mimetic thereof.

6. A polypeptide according to claim 5 for use in the prophylaxis or treatment of auto-immune disease such as rheumatoid arthritis.

7. A pharmaceutical composition comprising at least one polypeptide according to any of claims 1, 3 and 5 in combination with a pharmaceutically acceptable carrier or excipient.

8. A method of prophylaxis or treatment of auto-immune disease such as rheumatoid arthritis, which method comprises administering to a patient an effective amount of a polypeptide according to any one of claims 1, 3 and 5 or a pharmaceutical compositions according to claim 7.

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SEQ ID NO	SEQUENCE	GROUP
1	MAKTLAYDEEARRGL	1
2	AYDEEARRGLERGLNSL	
3	ARRGLERGLNSLADAVK	
4	ERGLNSLADAVKVTILGPKG	
5	SLADAVKVTILGPKGGRNV	
6	VKVTILGPKGGRNVVLEK	
7	GPKGGRNVVLEKKGWA	
8	NVVLEKKGWGA	
9	KKWGAPTTINDGVSI	
10	PTTINDGVSLAKEIEL	
11	DGYSLAKEIELDPYK	2
12	AKEIELDPYKIGAEIVK	
13	LEDPYKIGAEIVKEVAK	
14	EKIGAEIVKEVAKKTDDVA	
15	ELVKEVAKKTDDVAGD	
16	VAKKTDDVAGDGTITATVL	
17	DDVAGDGTITATVLAQALV	
18	DGTITATVLAQALVKEGL	
19	ATVLAQALVKEGLRNVAAGA	
20	QALVKEGLRNVAAGANPLG	
21	EGLRNVAAGANPLGLKRG	3
22	VAAGANPLGLKRGIEKA	
23	NPLGLKRGIEKAVDKV	
24	KRGIEKAVDKVTETL	
25	KAVDKVTETLLKDAK	
26	VTETLLKDAKEVETK	
27	LKDAKEVETKEQIAA	
28	EVETKEQIAATAAISA	
29	QIAATAAISAGDQSIGD	
30	TAAISAGDQSIGDLI	4
31	AGDQSIGDLIAEAMDKVG	
32	IGDLIAEAMDKVGN	
33	AEAMDKVGNVITV	
34	KVGNVITVEESNTFGL	
35	GVTVEESNTFGLQL	
36	EESNTFGLQLLQELTEG	
37	FGLQLLQELTEGMRFDKG	
38	ELTEGMRFDKGYISG	
39	MRFDKGYISGYFVTD	
40	GYISGYFVTDARQEA	

FIGURE 1(a)

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SEQ ID NO	SEQUENCE	GROUP
41	YFVTD AERQEAVLEEPYI	5
42	AERQEAVLEEPYILL	
43	AVLEEPYILLVSSKYSTVK	
44	PYILLVSSKYSTVKD	
45	VSSKYSTVKDLLPLEKV	
46	STVKDLLPLEKVIQAGK	
47	LLPLEKVIQAGKSLIITA	
48	EKVIQAGKSLIITAED	
49	AGKSLIITAEDVEGEAL	
50	LITAEDVEGEALSTL	
51	DVEGEALSTLVVNKIRG	6
52	ALSTLVVNKIRGTFKSA	
53	VVNKIRGTFKSAVKA	
54	RGTKSAVKAAPGFGD	
55	SAVKAAPGFGDRRKAMLQD	
56	APGFGDRRKAMLQDMAI	
57	DRRKAMLQDMAILTGAQV	
58	MLQDMAILTGAQVISEEVG	
59	ALTGAQVISEEVGL	
60	AQVISEEVGLTLENTDL	
61	EEVGLTLENTDLSLL	7
62	TLENTDLSLLGKARK	
63	DLSLLGKARKVVMTK	
64	GKARKVVMTKDETTIVEG	
65	VVMTKDETTIVEGAG	
66	DETTIVEGAGDTDALAG	
67	VEGAGDTDALAGRVA	
68	DTDALAGRVAQIRTEI	
69	AGRVAQIRTEIENS	
70	QIRTEIENS DSDYDREKL	
71	IENS DSDYDREKLQERL	8
72	SDYDREKLQERLAKL	
73	EKLQERLAKLAGGVAVIK	
74	RLAKLAGGVAVIKAG	
75	AGGVAVIKAGAATEV	
76	VIKAGAATEVELKERKHRI	
77	AATEVELKERKHRIEDA	
78	ELKERKHRIEDAVRNAK	
79	KHRIEDAVRNAKAAVEEG	
80	DAVRNAKAAVEEGIVAG	

FIGURE 1(b)

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SEQ ID NO	SEQUENCE	GROUP
81	AKAAVEEGIVAGGGV	9
82	EEGIVAGGGVTLLQAAPAL	
83	AGGGVTLLQAAPALDKL	
84	TLLQAAPALDKLKLITG	
85	APALDKLKLITGDEATG	
86	KLKLITGDEATGANTVKVA	
87	GDEATGANTVKVALEA	
88	GANTVKVALEAPLKQLA	
89	KVALEAPLKQLAFNSG	
90	APLKQLAFNSGMEPGV	
91	LAFNSGMEPGVVAEKV	10
92	GMEPGVVAEKVRNLSV	
93	VVAEKVRNLSVGHGL	
94	VRNLSVGHGLNAATG	
95	VGHGLNAATGEYEDL	
96	NAATGEYEDLLKAGVA	
97	EYEDLLKAGVADPVKV	
98	LKAGVADPVKVTRSAL	
99	ADPVKVTRSALQNAASLAG	
100	VTRSALQNAASLAGL	
101	LQNAASLAGLFLTTEA	11
102	SIAGLFLTTEAVVAD	
103	FLTTEAVVADKPEKTA	
104	AVVADKPEKTAAPASD	
105	KPEKTAAPASDPTGG	
106	AAPASDPTGGMCGMDF	

FIGURE 1(c)

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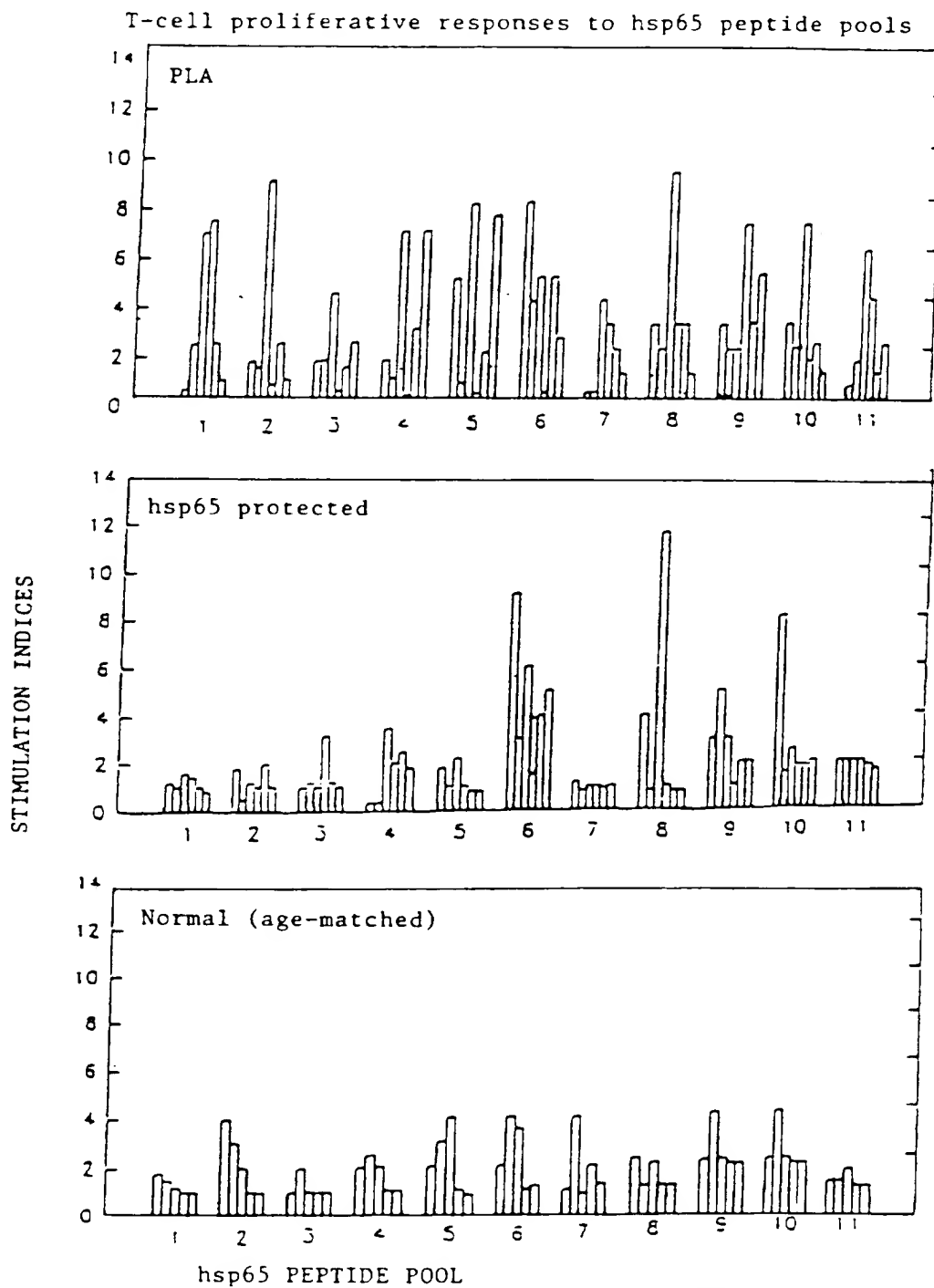
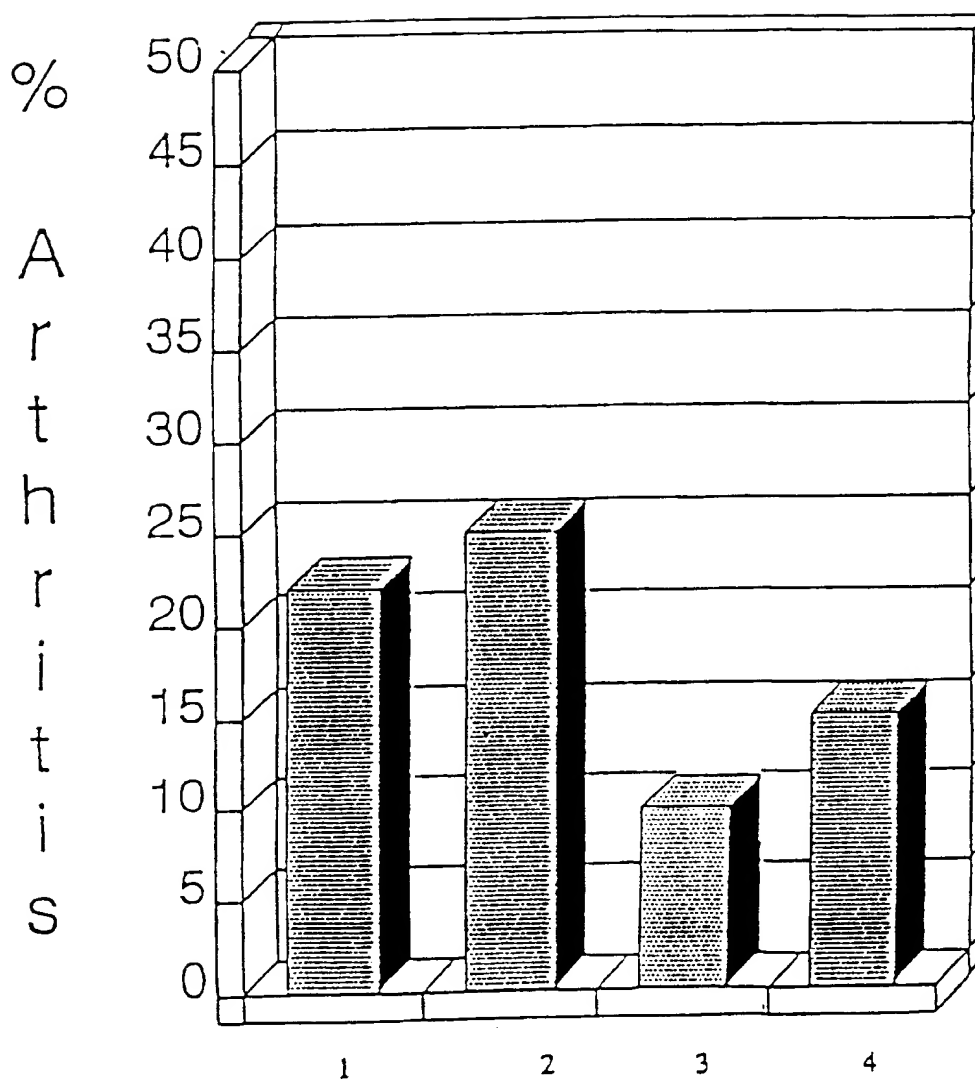


FIGURE 2

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FIGURE 3



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MLRLPTVFRQMRPVSRLAPHLTRAYAKDVKFGADARALMQGVOLLADAVAVTMGPGR 60
** : : ** :: * : ***** **:*****
mAKtiaydeeARRglerGlnaLADAVkVTlGPKGR 75

TVIIIEQSWGSFKVTKDGVIVAKSIDLKDKYKNIGAKLVQDVANNTNEEAGDGTTTATVLA 120
:; * * : * ****::** *: * * * * * : ** *: : *****
nvvlEkKwGaPtITnDGVsiAKeIeLeDpYekIGAeLVkeVAkkTdAvAGDGTTTATVLA 95

RSIAKEGFEXISKGANPVEIRRGVMLAVDAVIAELKKQSKPVTTPEEIAQVATISANGDK 180
::::* : ***** : ;** : ** : * * * * * * * * * *
galvrEGlrnvaaGANPlglkRGiekAVEkVtetLIKgaKeVeTkEgIAatAaISA-GDq 154

EIGNIISDAMKKVGRKGVITVKDGKTLNDELEIIIEGMKFDRGYISPYPINTSKGQKCEFO 240
:* : ** *** ** ; : **: ** : ***** ** : * ;
sIGdlIaeAMdKVGNegVITVeesntfIglgLEitEGMrFDkGYISgYFvtdperQeavle 214

DAYVLLSEKKISSIQSIVPALEIANAHRKPLVIIAEDVDGEALSTLVNLRLKVGLOVVAV 300
:; * * * : : :**** : *****:*****:****: : : *
DpYiLLvssKvStvkdlPlLEkvigagKPLIIAEDVGeGEALSTLVvNkirgtfkSVAV 274

KAPGFGDNRRKNQLKDMAIATGGAVFGEGLTLINLEDVQPHDLGKVGEVIVTKDDAMLLKG 360
***** * * * *****:** : ** : : * : * : ***** : : *

KAPGFGDrRKamLqDMAIlTGGoVisEE-vgLtLEnadlsllLGKarkVvVTkdettiveG 333

KGDKAQIEKRIQEIIIEQLDVTTSERVEKEKLNERLAKLS DGVAVLKVGGTSDVEVNEKKDR 420
* * * * : : : * : ***** ***** : * : : * : *
agDtDaIagrVaqrgeiensdSdYdrEKIqERLAKLagGVAVIKaGaateVELkErKhR 393

VTDALNATRAAVEEGIVLGGGCALLRCIPALDSLT PANEDQKIGIEIIKRTLKIPAMTIA 480
: * : : *****:*** * * : * * * : * * : * : * *
ieDAVrnakAAVEEGIVaGGGvtLLqaaPtLDaL-klegDeatGanIvKvaLeaPlkgIA 451

KNAGVEGSLIVEKIMQSSEVGYDAMAGDFVMVEKGIIDPTKVVRTALLDAAGVASLLT 520
* * * : : : * : * * * : : * : * * * * * * : * : * :
fNsGlEpgrvvaEKvrnlpaghGlnAqtGvyedllaGvaDPvKVtRsAlqnAAasiAgLf1 512

TAEVVVTEIPKEEKDPGMGAMGGMGGMGGM-F 573
* * : * * * : * * * * *
TtEaVVadkPekEKasvpG-----GGdM-GGMdF 540
taapasdpt---GG-M-GGMdF

FIGURE 4

SUBSTITUTE SHEET (RULE 26)

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PEPTIDES (251 - 312)

		% Homology
Myco 251-261	DVEGEALSTLV	
	* * : * * * * * *	~ 91%
Mamm 251-261	DVDGEALSTLV	
Myco 261-271	VVNKIRGTFKS	
	* : * : : : : :	~ 18%
Mamm 261-271	VLNRLKVGLQV	
Myco 272 - 281	VAVKAPGFGD	
	* * * * * *	100%
Mamm 272-281	VAVKAPGFGD	
Myco 282-296	RRKAMLQDMAITGG	
	** * * * * : * * *	75%
Mamm		
Myco 302-314	VGLTLENADLSL	
	: : * * * : :	~25%
Mamm 302-314	LTLNLEDVQPHD	

FIGURE 5

Effect of HSP peptide immunisation D=60
on PIA (% arthritis at D=210)

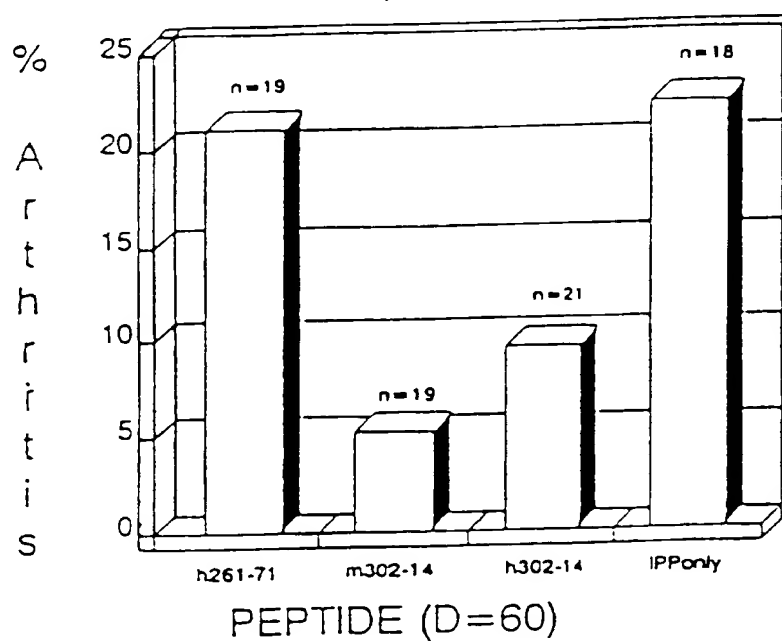


FIGURE 6

Effect of HSP peptide preimmunisation
on PIA (% arthritis at D=220)

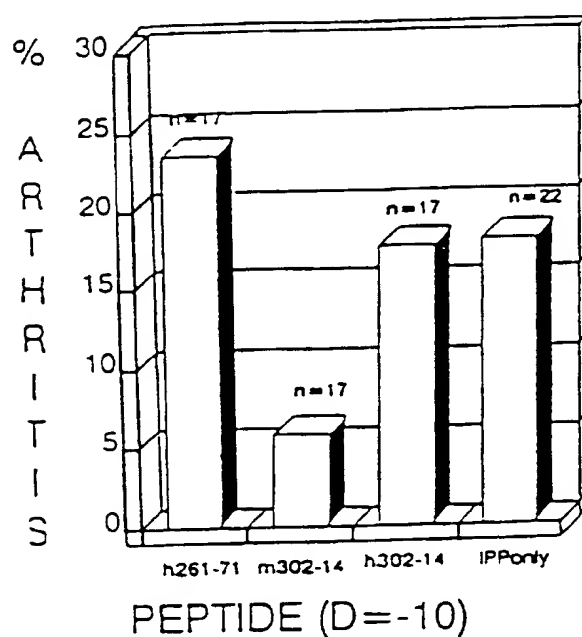


FIGURE 7

INTERNATIONAL SEARCH REPORT

International Application No.
PC 1/GB 96/02382

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07K14/35 C07K14/47 A61K38/17 A61K39/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07K A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 89 12455 A (WHITEHEAD INSTITUTE FOR BIOMEDICAL RESEARCH) 28 December 1989 see the whole document ---	1-8
A	WO 94 29459 A (WHITEHEAD INSTITUTE FOR BIOMEDICAL RESEARCH) 22 December 1994 see the whole document ---	1-8
P,X	WO 95 25744 A (RIJKSUNIVERSITEIT UTRECHT) 28 September 1995 see the whole document ---	1-8
P,X	WO 96 18646 A (REGENTS OF THE UNIVERSITY OF MINNESOTA) 20 June 1996 see the whole document -----	1-8

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

& document member of the same patent family

Date of the actual completion of the international search

24 January 1997

Date of mailing of the international search report

12.02.97

Name and mailing address of the ISA

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Moreau, J

INTERNATIONAL SEARCH REPORT

International application No.

PCT/GB 96/02382

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claim(s) 8
is(are) directed to a method of treatment of the human/animal
body, the search has been carried out and based on the alleged
effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such
an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all
searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment
of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report
covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is
restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No.

PCT/GB 96/02382

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO-A-8912455	28-12-89	AT-T- 127345	15-09-95
		CA-A- 1338778	10-12-96
		DE-D- 68924162	12-10-95
		DE-T- 68924162	25-04-96
		EP-A- 0419569	03-04-91

WO-A-9429459	22-12-94	EP-A- 0700445	13-03-96
		JP-T- 8510756	12-11-96

WO-A-9525744	28-09-95	AU-A- 1962895	09-10-95
		CA-A- 2185826	28-09-95
		EP-A- 0751957	08-01-97

WO-A-9618646	20-06-96	AU-A- 4518396	03-07-96

The first part of the paper discusses the importance of maintaining accurate records of all transactions. It is essential for the business to have a clear and concise record of all income and expenses, as this will be necessary for the preparation of the tax return. The second part of the paper discusses the importance of keeping up to date with the latest tax laws and regulations. It is important to consult with a tax professional to ensure that the business is compliant with all applicable laws. The third part of the paper discusses the importance of maintaining proper documentation for all transactions. This includes keeping receipts, invoices, and other documents that will be needed to support the tax return. The fourth part of the paper discusses the importance of keeping up to date with the latest tax software and programs. This will ensure that the business is able to calculate its tax liability accurately and efficiently. The fifth part of the paper discusses the importance of keeping up to date with the latest tax forms and schedules. This will ensure that the business is able to complete its tax return accurately and efficiently. The sixth part of the paper discusses the importance of keeping up to date with the latest tax rates and deductions. This will ensure that the business is able to take full advantage of all available tax benefits. The seventh part of the paper discusses the importance of keeping up to date with the latest tax credits and exemptions. This will ensure that the business is able to take full advantage of all available tax benefits. The eighth part of the paper discusses the importance of keeping up to date with the latest tax treaties and agreements. This will ensure that the business is able to take full advantage of all available tax benefits. The ninth part of the paper discusses the importance of keeping up to date with the latest tax court decisions and rulings. This will ensure that the business is able to take full advantage of all available tax benefits. The tenth part of the paper discusses the importance of keeping up to date with the latest tax legislation and regulations. This will ensure that the business is able to take full advantage of all available tax benefits.